Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Depressive symptoms evaluated by the Calgary Depression Scale for Schizophrenia (CDSS): Genetic vulnerability and sex effects

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ARTICLE INFO

Article history:
Received 1 April 2010
Received in revised form 9 November 2010
Accepted 11 November 2010
Available online xxxx

Keywords:
Depressive symptoms
Schizophrenia
Sex
Genetic

ABSTRACT

The present study compares the occurrence of depressive symptoms evaluated by the Calgary Depression Scale for Schizophrenia (CDSS) in patients of Multiplex (MS) and Simplex Schizophrenia families (SS). The Positive and Negative Syndrome Scale (PANSS) was used to evaluate psychopathology. A total of 206 paranoid schizophrenia patients were studied according DSM-IV criteria. The Family Interview for Genetic Studies (FIGS) was used to study the families. A result in the FIGS for a positive family history of schizophrenia was referred as MS (patients); its lack as SS (patients). CDSS scores were compared among MS and SS patients and possible sex differences intra- and inter-groups were explored. In the analysis of our sample (30) 19% of the total persons with schizophrenia group was depressed. The depressive symptoms measured by the CDSS were higher in females and the MS males group. Males from MS group showed more depressive symptoms than males from SS group. No differences with females from both groups were found. Findings in this study underscore the importance of gender and family history in understanding the heterogeneity of schizophrenia. This study suggests proved that sex and familiar history is an important point for studying depressive symptoms.

1. Introduction

Depression is a frequent symptom in schizophrenia. This observation was originally made by Bleuler, who considered anhedonia and disorders of affect to be important aspects of schizophrenia, and has continued to be recorded as definitions of schizophrenia have changed and evolved (Siris, 1991). The reported rate of depression is 7 to 75%, with a modal rate of 25% (Möller, 2005; Rocca et al., 2005; Maggini and Raballo, 2006). Depression symptoms are indeed frequent in schizophrenia in all the illness phases (Zisook et al., 2006). Differences in cohort status, illness chronicity and assessment methods contribute to the variability of these estimates (Rocca et al., 2005).

There are contradictory findings on the origins of depressive symptoms in schizophrenia. There are several hypotheses that explain depression in schizophrenia which support those depressive symptoms may have a multifactorial etiology: they may be a part of the pathology or they may be reactive post-psychotic, pharmacogenic or akinetic (Bressan et al., 2003).

Some evidences support the hypothesis that depressive symptoms are an integral part of schizophrenia (Bressan et al., 2003). Depressive symptoms in schizophrenia spectrum disorders are not an epiphenomenon; it is more a primary disorder with the same origins as the depressive disorder itself (Bressan et al., 2003). Studies performing symptoms factor analysis in large samples of patients consider depressive symptoms as one of the psychopathological domains of schizophrenia in addition to positive, negative, excitement and cognitive domains (Cuesta and Peralta, 2001).

Depressive symptoms have been associated to several negative aspects of the clinical outcome, including cognitive impairment, deterioration of psychosocial functioning, increased relapse risk, longer hospitalization periods, poorer response to medication, chronicity and increased suicide risk (Bressan et al., 2003). However, the two most frequently used diagnostic classifications in psychiatry, DSM-IV (American Psychiatric Association, 1994) have not identified depressive episodes in the majority of clinically stable schizophrenia patients (Bressan et al., 2003). ICD-10 has a specific diagnostic criterion for depression in schizophrenia called post-schizophrenic depression. On

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doi:10.1016/j.psychres.2010.11.026

the other hand, DSM-IV does not have any category in the main classification (Bressan et al., 2003). This has research and clinical implications. In the clinic side, faithful adherence to the present classification system could lead to misdiagnosis and under-treatment of depressive episodes in schizophrenia.

Depression occurring in schizophrenia is a common problem; however, investigators have typically not studied it with the paranoid/nonparanoid dichotomy in mind. The reports of depression for different types of schizophrenia have been contradictories. For example, it has been found that patients with a paranoid type of schizophrenia were the least depressed and had the fewest fluctuations of mood (Strian et al., 1981). But a very different idea was presented in another study: depressed mood and anhedonia constitute serious problems for schizophrenia patients, particularly for paranoid schizophrenia patients during the postpsychotic phase of their illnesses (Candido and Romney, 2002).

The 1933 introduction of schizoaffective disorder recognized the diagnostic relevance of mood symptoms in psychotic patients, linked schizophrenia (psychosis) and mood disorders, and eroded the concept of the Kraepelinian dichotomy. Some authors now consider schizoaffective disorder to be a psychotic mood disorder and not a subtype of schizophrenia or a separate disorder. In addition, certain investigators have associated paranoia with depression and delusional guilt (Lake, 2008).

Comparative clinical and recent molecular genetic data find phenotypic and genotypic commonalities between patients diagnosed with schizophrenia and psychotic bipolar disorder supporting the idea that paranoid schizophrenia could be the same disorder as psychotic bipolar disorder (Lake, 2008). On the other hand, recent study reported cognitive and emotion-related processes are involved in paranoid delusions (Bentall et al., 2009).

The Calgary Depression Scale for Schizophrenia (CDSS) has emerged as a valid instrument for assessing depressive symptoms in schizophrenia (Addington et al., 1993). This scale enables depression to be assessed independently of negative or extrapyramidal symptom-related depressive phenomena in schizophrenia (Addington et al., 1994). Psychometric properties of the CDSS have been widely documented in stabilized patients (Collins et al., 1996; Kontaxakis et al., 2000; Lancon et al., 2001; Kim et al., 2006).

In schizophrenia, not all clinical dimensions related to genetic vulnerability are equally reported. For example, in the case of negative symptoms, they are probably more heritable and may have stronger genetic bases than positive symptoms (Dworkin and Lenzenweger, 1984; Martin et al., 2004).

There are projects examining the relationship between depressive symptoms measured by CDSS with the Positive and Negative Syndrome Scale (PANSS) (Collins et al., 1996; Kim et al., 2006). The depression scale was found to be highly correlated with the negative symptoms subscale (Kontaxakis et al., 2000; Rocca et al., 2005). However, other studies reported correlation with positive, negative and general psychopathology (Lancon et al., 2001).

Many studies support the presence of significant differences between males and females with schizophrenia arising from the interplay of sex hormones, neurodevelopmental and psychosocial sex differences (Leung and Chue, 2000). Sex differences in schizophrenia have been associated with the onset year and the course in cognitive and neuropsychological functioning (Bozikas et al., 2006; Weiss et al., 2007). Studies on affective disorders without psychotic features report a sex ratio for depression in females – males equal to 1.5–3:1 (Angst et al., 2002; Marcus et al., 2005). With these numbers, it is possible that partly different biological mechanisms in females and males with schizophrenia are involved, and they could also lead to different depression phenomena.

Schizophrenia is a complex, multifactorial and polygenic disease (Thibaut, 2006). Therefore, the distribution of impairment among schizophrenia families is consistent with multifactorial models of familial transmission. Presumably, families with more than one affected or Multiplex Schizophrenia (MS) families have more genetic susceptibility to the illness than families with just one affected or Simplex Schizophrenia (SS) families, putting relatives at greater risk for MS families (Seidman et al., 2003). It is hypothesized that the higher the number of affected members in a family (MS), the more likely they are to have a genetic vulnerability to the illness, while those patients belonging to the group with a negative family history are considered to have a more environmental form and less genetic vulnerability (Tsuang et al., 2006).

Peralta and Cuesta (2007), reported in a familial liability study that categories of psychotic disorders are on a continuum of familial liability to schizophrenia and mood disorder. “More specifically, a relative broad phenotype either early age or lack of affective features appears to be closer to familial liability than the highly restrictive phenotypes such as DSM-IV and Kraepelian diagnostic concepts” (Peralta and Cuesta, 2007).

That is why the purpose of this study is to research the pattern of occurrence and features associated with depressive symptoms evaluated by the Calgary Depression Scale for Schizophrenia (CDSS) in schizophrenia patients from MS and SS families and its relation with the sex factor.

2. Methods

2.1. Subjects

A total of 206 paranoid schizophrenia outpatients in the stable period were recruited from 3 community mental health centers in Havana City. Patients were selected only from families who agreed to participate. A written informed consent was obtained from the families. Only 31.6% outpatients or families from community mental health centers refused to participate and 9.1% left the study.

Diagnoses were confirmed using the Spanish version of the semi-structured clinical interview: Present State Examination (PSE-10) was based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) created by the World Health Organization (WHO) (Vázquez- Barquero, 1992). This study is part of a family study to search for endofenotypes in schizophrenia organized by Cuban Neuroscience Center. Schizophrenia was considered stabilized if patients had their antipsychotic regimen unchanged for the last 6 months and were judged clinically stable by the specialists from community mental health centers. Were excluded from the study patients with alcoholism, substance abuse, and other organic causes of depression.

The interviewers were psychiatric specialists previously trained by the WHO in the SCAN system. The convergence in the classification by the two measures was calculated by Kappa (K). Inter-rater reliability was high for the overall diagnostic (kappa coefficient = 0.70) (Martin et al., 1997). The diagnostic criteria applied were those of the DSM-IV (American Psychiatric Association, 1994). All the patients accepted and signed the terms of the informed consent to participate in the study. The research reported in this article was reviewed and approved by the Cuban Neuroscience Center Research Board and is in compliance with the ethical rules for human experimentation as stated in the Declaration of Helsinki.

2.2. Clinical assessments

Depressive symptoms were evaluated using the Spanish version of the CDSS (Sarro et al., 2004). CDSS is an observer scale, based on semi-structured, goal-directed interviews, specifically developed for the assessment of the level of depression in schizophrenia. The presence or absence of clinically significant depression was determined using a cut-off point ≥ 6 (Addington et al., 1992).

The Spanish version of the PANSS (Kay,1987) was used to evaluate positive and negative symptoms and general psychopathology. The interviewers were psychiatric specialists previously trained in the use of this scales.

2.3. Family study

The Family Interview for Genetic Studies (FIGS) (NIMH-Molecular Genetics Initiative, Maxwell 1992) was used for the family study. The FIGS is a guideline used to gather diagnostic information on the relatives of patients with schizophrenia and bipolar disorders. A genealogical tree was constructed before applying this instrument and it was reviewed with the participants. For each subject, at least two non-affected key informant first degree relatives were interviewed by a psychiatric specialist trained to use the instrument, (blind to Calgary results). In this study we used the Spanish version validated in our country (Diaz de Villalvilla et al., 2008).

None of the informants were diagnosed with schizophrenia related disorders according to the FIGS interview. Family history information was complemented by

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medical records. Final diagnoses for DSM-IV schizophrenia in relatives were made by a psychiatrist based on the all available data.

We calculated the family loading (FL) as described in Verdoux et al. (1996). For schizophrenia, 15-years-old or younger subjects were not included in the analysis (weight = 0). Subjects ranging from 15 to 45 and those over 45-years-old at the time of the evaluation were weighted 0.5 and 1, respectively. FL scores were calculated by taking into account information derived from first degree relatives. FL scores were used to separate groups of patients according to their familial aggregation: "Simplex Schizophrenia" (FL < −0.5) or "Multiplex Schizophrenia" (FL > 3) or ambiguous cases (FL between −1 and 3). The last group (ambiguous) was not used in this analysis (in our study, we used FL as a categorical variable). FL scores were compared between the two groups of subjects using analysis of variance. We kept in mind that there were no differences as far as the number of relatives reported in the genealogical trees in either group (MS or SS) and that the number of reported generations in the genealogical tree was more than three in both groups.

2.4. Statistical analysis

The continuous variables are expressed as means ± S.D. and the categorical variables as frequencies. Differences between groups (MS vs. SS) and sex were tested with ANOVA for continuous variables. Chi-square test (χ^2) with Yates's correction was used in order to compare categorical variables between groups. The sums of the items of each subscale of the CDSS were used in the analysis. Mann–Whitney *U* test was used for comparison of CDSS and PANSS scores between MS and SS patients. Pearson's correlation coefficients were conducted to examine the relationship between the rating of CDSS and PANSS subscales. CDSS items were subjected to a principal components analysis (PCA) followed by Varimax rotation and simple clustering. Factorial Anova were conducted to analyze the higher-order interactive effects of multiple categorical independent variables. The Varimax method was used to rotate the factors. The data analysis was carried out using Statistics for Windows (v.6.1) software (StatSoft, Inc. 2003). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Sociodemographic data

The studied population consisted of 206 paranoid schizophrenia patients providing 206 schizophrenia families interviewed. According to the familiar aggregation type, 101 (49%) families were classified as MS and 105 (51%) as SS.

Sample characteristics are shown in Table 1. Sociodemographic characteristics (age, gender, race, education and marital status) and disease associated variables (age of onset and duration) were not significantly different between Multiplex and Simplex persons with schizophrenia. The 92% of participants were under typical neuroleptic medication, and no significant differences between MS and SS patients were found for medication type.

The number of individuals reported in the genealogical trees resulting of FIGS did not differ significantly between MS and SS.

Significant differences in Age of onset and Marital Status were found between sex groups. Not significant differences between sexes were found for medication type, age, race and education level. The mean ratings of Age of onset (years) in females was Mean ± S.D. (23.6 ± 7.0) and (20.0 ± 5.7) in males, $p = 0.0006$. Marital Status was also significantly different between females/males, the proportion of females married was significantly higher 43(67%) compared with the males 21(33%), $p = 0.006$.

3.2. Clinical characteristics

The mean ratings of CDSS and PANSS for MS and SS groups are shown in Table 2. Mann–Whitney *U* test confirmed a highly significant difference between groups for CDSS scores. Items (1) Depressed mood, (2) Hopelessness, (3) Self depreciation, and (9) Observed depression was more severe in MS than SS patients (p values in Table 2). The analysis also revealed that MS showed greater severity of negative subscale and total PANSS scores than SS patients (p values in Table 2).

The differences in negative symptoms are given by the familial aggregation factor and not by sex. Factorial Anova to analyze the higher order interactive effects of multiple categorical independent variables showed no significant differences between PANSS subscales and sex ($F = 1.70$, d.f. = 4, $P = 0.150$). The variables sex, PANSS and MS vs. SS did not show significant difference ($F = 0.35$, d.f. = 4, $P = 0.839$). The analysis revealed ratings for negative symptoms were also significantly different between MS vs. SS groups ($F = 3.96$, d.f. = 4, $P < 0.001$).

Table 1
Sample characteristics.

Variables	Total sample	Multiplex patients	Simplex patients
n	206	101	105
Age (years) Mean ± S.D.	40.75 ± 13.1	42.05 ± 14.3	39.49 ± 11.7
Gender *n* (%)			
Female	89(43.2)	43(42.6)	46(43.4)
Male	117(56.7)	58(57.4)	59(56.2)
Race *n* (%)			
White	160(76.6)	77(76.2)	83(79.0)
Mulato	23(11.2)	14(13.8)	9(8.6)
Black	23(11.2)	10(10.0)	13(12.4)
Education (years) Mean ± S.D.	9.65 ± 3.0	9.60 ± 2.9	9.70 ± 3.6
Marital status *n* (%)			
Married	64(31.1)	34(33.7)	30(28.6)
Not married	142(68.9)	67(66.3)	75(71.4)
Age of onset (years) Mean ± S.D.	21.65 ± 6.8	21.6 ± 7.7	21.68 ± 5.8
Duration of ill (years) Mean ± S.D.	18.13 ± 12.4	18.9 ± 13.9	17.4 ± 10.9
Antipsychotic treatment *n* (%)			
Typical neuroleptics	190(92.2)	91(90.1)	99(94)
Atypical neuroleptics	16(7.5)	10(9.9)	6(6)
Number of individuals in the genealogical tree (FIGS) Mean ± S.D.	26.8 ± 16.7	28.3 ± 15	25.7 ± 17

3.3. Depressive symptoms in Multiplex and Simplex Schizophrenia patients related to sex

Factorial ANOVA of CDSS total scores for Multiplex and Simplex Schizophrenia showed a different behavior in terms of gender. A significant difference of means of CDSS score between subgroups was found significantly more severe in female patients form MS and SS than male from SS. However, males from MS had more depressed symptoms than SS males. ($p = 0.03$). Fig. 1.

A ≥6 CDSS total score was considered indicative of depression according to Addington et al., 1993. In the cross-sectional analysis

Table 2
Mean ratings of Calgary Depression Scale for Schizophrenics (CDSS) and Positive and Negative Syndrome Scale (PANSS) for Multiplex and Simplex Schizophrenia patients.

	Multiplex schizophrenia (Mean ± S.D.)	Simplex schizophrenia (Mean ± S.D.)	*p* values
CDSS (items) symptom			
(1) Depression mood	0.853 ± 0.942	0.469 ± 0.759	**0.001***
(2) Hopelessness	0.847 ± 0.967	0.481 ± 0.760	**0.003***
(3) Self depreciation	0.836 ± 1.045	0.506 ± 0.776	**0.031***
(4) Guilty ideas of reference	0.372 ± 0.766	0.407 ± 0.754	ns
(5) Pathological guilt	0.316 ± 0.791	0.296 ± 0.679	ns
(6) Morning depression	0.361 ± 0.741	0.246 ± 0.536	ns
(7) Early wakening	0.327 ± 0.703	0.370 ± 0.660	ns
(8) Suicide	0.338 ± 0.737	0.271 ± 0.612	ns
(9) Observe depression	0.593 ± 0.841	0.358 ± 0.657	**0.044***
Total CDSS	4.841 ± 5.705	3.407 ± 4.813	0.05
PANSS subscales			
Positive	21.7 ± 11.6	19.9 ± 10.7	ns
Negative	24.3 ± 10.6	19.3 ± 8.8	**0.007***
General psychopathology	36.5 ± 13.1	34.9 ± 12.0	ns
Total PANSS	82.6 ± 27.4	74.2 ± 27.5	**0.038***

*$p < 0.05$ are considered statistically significant, and resulted from the scores comparison between groups using the Mann–Whitney *U* test.

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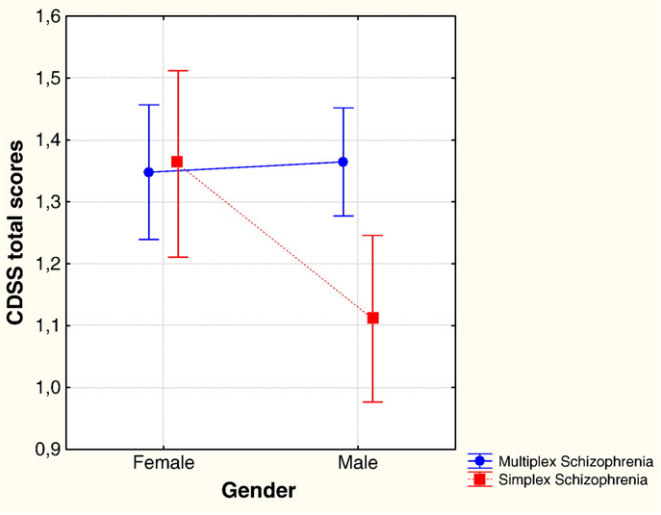

Fig. 1. Factorial ANOVA of CDSS total scores for multiplex vs. simplex schizophrenia according to gender.

30.19% of the total sample scored as depressed. The depression symptoms measured by CDSS was higher in MS compared with SS patients (Chi-square test, $\chi^2 = 4.73$; d.f. = 1; $p < 0.029$).

The comparison of MS and SS females did not show significant differences (Chi-square test, $\chi^2 = 0.006$; d.f. = 1; $p = 0.94$). However, the comparison of MS and SS males showed significant differences between groups (Chi-square test, $\chi^2 = 8.7$; d.f. = 1; $p < 0.003$), with higher depression symptoms in MS.

According to this findings, SS females showed significantly higher depression symptoms than SS males (Chi-square test, $\chi^2 = 5.86$; d.f. = 1; $p < 0.01$), while MS male and female groups did not have any differences in terms of depression (Chi-square test, $\chi^2 = 0.004$; d.f. = 1; $p = 0.94$). The depressed group (CDSS total score > 6) showed a significantly higher number of psychosis relatives in their families observed in the genealogical tree ($p < 0.001$).

3.4. Factor analysis by CDSS

The results of Varimax rotated CDSS factor analysis are presented in Table 3. We found two factors: factor one was related to the items 1. Depressed mood, 2. Hopelessness, 3. Self depreciation, 4 Guilty ideas of reference, 4. Pathological guilt and 9. Observed depression. Factor two was related to items 6. Morning depression and 7. Early wakening. The resulting solution explained 68% of the variance in scores.

3.5. Correlations between CDSS and PANSS

Pearson's coefficients of correlations between scores on the CDSS and PANSS in Multiplex and Simplex Schizophrenia patients are summarized here. There were significant correlations among General psychopathology subscale PANSS, and the majority of depressive symptom items rated with CDSS in MS and SS groups. Item 6 (Morning depression), was significantly correlated with positive subscale PANSS in MS patients(0.24, $p = 0.009$) and Item 3 (Self depreciation) (0.22, $p = 0.015$), was significantly correlated with negative subscale PANSS in MS patients.

Table 3
Factor analysis of Calgary Depression Scale for Schizophrenia (CDSS).

Symptom	Factor 1	Factor 2
1. Depressed mood	**0.67**	0.57
2. Hopelessness	**0.67**	0.54
3. Self depreciation	**0.70**	0.50
4. Guilty ideas of reference	**0.85**	0.14
5. Pathological guilt	**0.90**	0.12
6. Morning depression	0.12	**0.75**
7. Early wakening	0.08	**0.75**
8. Suicide	0.36	0.46
9. Observe depression	**0.65**	0.62

Items loading above 0.65 are in bold.

4. Discussion

4.1. Depression symptoms in multiplex vs. simplex schizophrenia

Our findings suggest that depression is an important clinical phenomenon in schizophrenia. It was interesting to find out that the depression symptoms measured by CDSS was higher in male MS patients compared to SS patients. The CDSS items accounting for this difference (*depressed mood/hopelessness/self-depreciation/observed depression*) have been referred as belonging to factor I. Only two items of factor I in our study do not differ significantly.

The CDSS Factor 1 is considered a "general depression factor" and is closely linked to depression cluster itself in schizophrenia (Addington et al., 1996). Our result is different from the factor analysis in Addington's study, they found three factors and we found two. However, 4 items (*depressed mood/hopelessness/self depreciation/pathological guilt*) of the Factor 1 of the results in Addington study are consistent with factor I of our study. We did not find differences between groups with factor II (*Morning depression/Early wakenig*). Early wakening is part of factor 3 in Addington's study: they analyze the clinical significance of this items is different from factor 1, early wakening is a symptom of melancholia, which is specific for a mayor depressive episode.

Schizophrenia is seen as a "family of disorders" that is mediated by complex genetic vulnerability and gene–environment interactions. Interestingly enough, all these disorders may be attributable to a complex interplay of vulnerability genes that predispose an individual to develop the disease and to nongenetic "second hits" that precipitate the disorders (Braff and Light, 2005). It is proposed that in families with history of schizophrenia (MS) the genetic loading or risk is stronger and that the possibilities to find genetic liability associated deficits are higher. Following this idea, abnormalities such as sustained attention along with perceptual load processing (Tsuang et al., 2006) and abnormal saccadic eye movements (Schwartz et al., 1995) have been described in MS.

This assumption may be the cornerstone of the finding of higher ratings of depression symptoms in MS and it should indicate a relationship between depression cluster and vulnerability genes in the illness.

This assumption can be related to other findings in families with a positive history of schizophrenia. Several schizophrenia family studies report increased risk for recurrent unipolar depression and schizoaffective disorders among relatives of schizophrenic probands (Braff and Light, 2005). Other studies have found an increased risk for psychotic affective disorders among the relatives of schizophrenic probands (Taylor et al., 1993; Braff and Light, 2005). Results from anticipation studies in schizophrenia have suggested that the phenotype progressed from affective disorder to schizophrenia (Basset and Husted, 1997) thus, the hypothesis of an association between genetic factors and depression cluster in schizophrenia is reasonable.

4.2. Depression symptoms and PANSS

The present study found greater severity of negative symptoms and total PANSS scores in MS than SS patients. Differences in total PANSS scores between MS and SS patients may be a reflection of the differences in the negative symptoms between groups. More prominent negative symptoms in MS are generally consistent with

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the hypothesis that increased genetic liability to schizophrenia is related to negative dimension. The first major report linking negative symptoms and genetic influences in schizophrenia was in Dworkin and Lenzenweger (1984). They found that concordance rates in monozygotic twins were significantly higher when probands had a greater number of negative symptoms but that there was no evidence of a similar relationship between positive symptoms and concordance rates. Other authors have also reported that negative symptoms are more severe in schizophrenia patients with affected relatives and are also present in some non-schizophrenic relatives of patients with schizophrenia (Tsuang et al., 2000). Such findings are consistent with the strong heritability component for negative symptoms demonstrated by twin studies (Malaspina et al., 2000).

The negative symptom syndrome of schizophrenia overlaps with the syndrome of depression in a number of important respects. Diminished interest, pleasure, energy, or motivation along with psychomotor retardation and impaired ability to concentrate are relevant overlapping features. However, certain other symptoms may be more distinguishing. Blunted affect, for example, suggests negative symptoms, whereas distinct blue mood or cognitive features such as guilt or suicidal thoughts suggest depression. Unfortunately, differentiating these two states can sometimes be difficult if patients lack the interpersonal communication skills to articulate their internal subjective states well (Siris, 2000).

The CDSS scale was unique in its ability to discriminate between depression and negative symptoms (Addington et al., 1996; Collins et al., 1996; Kontaxakis et al., 2000; Kim et al., 2006). We found a high correlation index between general psychopathological subscale (PANSS) and CDSS in MS and SS patients. In our study we did not find significant correlations between positive and negative subscales of PANSS and CDSS, we only found significant correlations between item 6 (Morning depression with positive subscale) and item 3 (Self depreciation, with negative subscale). The general psychopathology subscale of PANSS showed high correlations with CDSS in MS and SS patients. On this point we think that the general psychopathology subscale of PANSS measures symptoms of depression and anxiety that correlate with depressive symptoms (Möller, 2005). Some studies have reported that the relationship between depression symptoms measured by CDSS and other symptoms of schizophrenia appear to differ during different stages of the illness (Lancon et al., 2001).

The CDS has been validated in different languages (Brazilian, Danish, French.). It has been shown that there is no overlap between negative or extrapyramidal and depressive symptoms patients. However, these specific scales are rarely used in clinical practice. Only about 1% of the US psychiatrists reported the use of the Calgary Depression Scale (Micalle et al., 2006).

4.3. Sex differences

Literature involving differences between males and females in schizophrenia continues to grow. Many studies support the notion that male patients may have a more severe manifestation of the illness than female patients (Leung and Chue, 2000). Males have a poorer premorbid adjustment, more negative symptoms, a poorer response to treatment and a greater severity of brain abnormalities (Nopoulos et al., 1997).The earlier age of onset of schizophrenia in males compared to females by 3–5 years, is a consistent finding across many studies (Leung and Chue, 2000). This finding is replicated in our study. The proportion of married women in our study was higher than in men. Men with schizophrenia have poorer social functioning than women across various domains (Leung and Chue, 2000). Males show more negative symptoms in many studies (Nopoulos et al., 1997; Leung and Chue, 2000). However, in our sample, the differences in negative symptoms were reported by the familial aggregation and not by sex.

As far as we know, different results in schizophrenia patients according to depression symptoms, positive family history of schizophrenia, and gender have not been reported. In this study, females were associated with more depression symptoms and this finding was independent from familial aggregation type. This result is consistent with other studies that have proved that females display more depressive symptoms than males (Goldstein, 2006). Other studies have reported that schizophrenia in women appears to be characterized by greater affective symptoms such as dysphoria, depression, irritability and inappropriate affection (Leung and Chue, 2000). MS males and MS females showed no significant differences regarding depressive symptoms. However, SS males showed significantly lower depression symptoms compared to SS females. This result may be indicative of the relationship between presence of depression symptoms in males and family history of the disease.

A proposed explanation is related to the fact that estrogens have several antidopaminergic actions that can bring protection against psychosis in females (Goldstein, 2006). However, in the case of depression symptoms the female sex was not a protective factor. This fact may mean that the protective mechanism associated to females for psychosis, possibly hormonal, has no effect on depression symptoms. On the other hand, in MS the advantages of SS males (lower presence of depression symptoms) compared to SS females disappear. In case there is some genetic vulnerability for schizophrenia associated to depression symptoms, it is increased in MS patients; therefore there may reasonably be a higher frequency of depression in MS males.

4.4. Study limitations

Our results should be interpreted in the context of two basic methodological limitations.

The strategy of differentiating Multiplex vs. Simplex families has been reported as having little influence and showing little sensitivity by some authors (Roy and Crowe, 1994; Malaspina et al., 1998). One possible contributor to this particular problem is that MS families might be reported as SS due to the lack of sufficient family history information or studying only a few generations in the family evaluation. In this study, the number of individuals reported in the genealogical tree (FIGS) was not significantly different between Multiplex and Simplex Schizophrenia. Furthermore, more than three generations were reported in the genealogical trees and FIGS data were collected from no less than two participants per family. An analysis of family loading for schizophrenia indicates that the "Simplex Schizophrenia" report was not influenced by the size and structure of the families in our research.

Antipsychotic treatment made it difficult to determine what was responsible for the depressive symptoms. The use of typical neuroleptics has been related to depressive symptoms (Kaneda, 2003). Bressan suggests that high striatal dopamine D2 blockade by typical antipsychotic drugs may contribute to the emergence of depressive symptoms in typical antipsychotic treated schizophrenia patients (Bressan et al., 2002). On the other hand, atypical antipsychotics seem to be more favourable in treating depression in schizophrenia (Tollefson et al., 1998). In our sample, patients were chronically medicated, but MS and SS groups did not differ in type of antipsychotic treatment used; therefore, differences found between MS and SS groups are not related to the type of medication. However, the lack of assessment of side-effects and detailed medication regimens could be confounding factors. Another limitation of this study is that the sample was limited only to paranoid schizophrenia.

4.5. Summary

The depressive symptoms measured by the CDSS were higher in females and the MS males group. Males from MS group showed more

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depressive symptoms than males from SS group. No differences with females from both groups were found.

This study suggests that sex and familiar history is important point for depressive symptoms.

The presence of depressive symptoms in schizophrenia varies widely in literature (Lancon et al., 2001). The discrepancy observed between our findings and previous studies may be due to the fact that the other studies do not explore the positive family history of schizophrenia. In future studies, considering family history may become an important strategy for studies of depression in schizophrenia.

The higher ratings of depression and its similar frequency between males and females in MS should indicate a relationship between depression cluster and vulnerability genes in schizophrenia. Then, the selection of subgroups of MS patients with higher CDSS scores may result in more homogeneous samples with important utility for the genetic research of the illness.

Depressive symptoms require specific pharmacological and psychotherapeutic treatment. Restricting the diagnosis of depressive symptoms to the post-psychotic period may lead to misdiagnosis and undertreatment in a large number of cases. Disparities in treatment approaches varying from the existing scientific evidence base underscore the need for further investigation into ways of optimizing the management of depression in schizophrenia (Siris, 2000) Depressive symptoms need continued systematic investigation in schizophrenia, particularly in view of their relevance to genetic research.

Conflict of interest

None to declare.

Acknowledgments

This study was supported in part by a grant from the Cuban Academy of Sciences on the topic "Endophenotypes in Schizophrenia" and funds from the Cuban Neuroscience Center. The manuscript preparation received financial support from the Royal Society.

The authors would like to thank the staff of the community mental health centers in Havana City for their help in collecting the research data. We are grateful to all the families participating in this study.

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Please cite this article as: Martín-Reyes, M., et al., Depressive symptoms evaluated by the Calgary Depression Scale for Schizophrenia (CDSS): Genetic vulnerability and sex effects, Psychiatry Res. (2010), doi:10.1016/j.psychres.2010.11.026

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